```
=> e tpa/cn
E1            1     TP73L PROTEIN (DANIO RERIO CLONE MGC:92012 IMAGE:7043854)/CN
E2            1     TP75 PROTEIN (TREPONEMA PALLIDUM GENE TP0006)/CN
E3            4 --> TPA/CN
E4            1     TPA (PHORBOL DERIVATIVE)/CN
E5            1     TPA 10/CN
E6            1     TPA 100/CN
E7            1     TPA 330/CN
E8            1     TPA 36/CN
E9            1     TPA 4380/CN
E10           1     TPA 4390/CN
E11           1     TPA 50/CN
E12           1     TPA 5028/CN

=> s e4
L1            1 "TPA (PHORBOL DERIVATIVE)"/CN

=> d l1 1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   16561-29-8  REGISTRY
CN   Tetradecanoic acid, (1aR,1bS,4aR,7aS,7bS,8R,9R,9aS)-9a-(acetyloxy)-
     1a,1b,4,4a,5,7a,7b,8,9,9a-decahydro-4a,7b-dihydroxy-3-(hydroxymethyl)-
     1,1,6,8-tetramethyl-5-oxo-1H-cyclopropa[3,4]benz[1,2-e]azulen-9-yl ester
     (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1H-Cyclopropa[3,4]benz[1,2-e]azulene, tetradecanoic acid deriv.
CN   Myristic acid, 9-ester with 1,1aα,1bβ,4,4a,7aα,7b,8,9,9a-
     decahydro-4aβ,7bα,9β,9aα-tetrahydroxy-3-
     (hydroxymethyl)-1,1,6,8α-tetramethyl-5H-cyclopropa[3,4]benz[1,2-
     e]azulen-5-one 9a-acetate, (+)- (8CI)
CN   Tetradecanoic acid, 9a-(acetyloxy)-1a,1b,4,4a,5,7a,7b,8,9,9a-decahydro-
     4a,7b-dihydroxy-3-(hydroxymethyl)-1,1,6,8-tetramethyl-5-oxo-1H-
     cyclopropa[3,4]benz[1,2-e]azulen-9-yl ester, [1aR-
     (1aα,1bβ,4aβ,7aα,7bα,8α,9β,9a.alpha
     .)]-
OTHER NAMES:
CN   β-Phorbol 12-myristate 13-acetate
CN   12-O-Tetradecanoylphorbol 13-acetate
CN   12-Tetradecanoylphorbol 13-acetate
CN   12-Tetradecanoylphorbol 13-monoacetate
CN   13-O-Acetylphorbol 12-myristate
CN   4β-Phorbol 12-myristate 13-acetate
CN   Factor A1
CN   Factor A1 (croton oil)
CN   NSC 262244
CN   Phorbol 12-myristate 13-acetate
CN   Phorbol 12-tetradecanoate 13-acetate
CN   Phorbol myristate acetate
CN   PMA
CN   PMA (tumor promoter)
CN   TPA
CN   TPA (phorbol derivative)
AR   27936-27-2
FS   STEREOSEARCH
DR   11016-13-0, 11019-85-5, 20839-11-6, 26894-58-6, 27534-73-2
MF   C36 H56 O8
CI   COM
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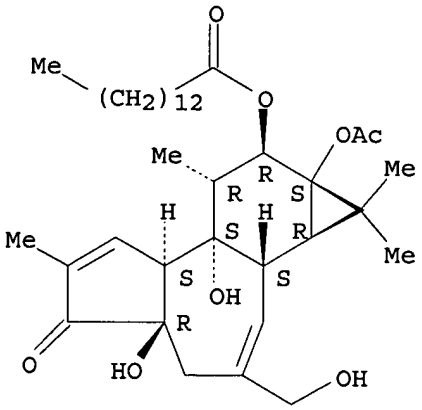
LC STN Files: ADISNEWS, AGRICOLA, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, MEDLINE, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

12790 REFERENCES IN FILE CA (1907 TO DATE)
28 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12800 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

```
=> d his

     (FILE 'HOME' ENTERED AT 22:00:37 ON 03 MAR 2005)

     FILE 'REGISTRY' ENTERED AT 22:01:00 ON 03 MAR 2005
                E TPA/CN
L1             1 S E4

     FILE 'MEDLINE, HCAPLUS, CANCERLIT' ENTERED AT 22:04:04 ON 03 MAR 2005

=> s l1 and prostat? and (neoplas? or tumor? or tumour? or cancer? or adenom? or
hyperplas?)
L2           227 L1 AND PROSTAT? AND (NEOPLAS? OR TUMOR? OR TUMOUR? OR CANCER?
                 OR ADENOM? OR HYPERPLAS?)

=> s l2 and (paclitaxel? or retinoid? or retinoic? or atra or trans(3a)retinoi?)
L3            13 L2 AND (PACLITAXEL? OR RETINOID? OR RETINOIC? OR ATRA OR TRANS(3
                 A) RETINOI?)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4             9 DUP REM L3 (4 DUPLICATES REMOVED)

=> d l4 abs cbib kwic 1-9

L4   ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2005 ACS on STN
AB   Mitogen-activated protein (MAP) kinases (e.g., ERK1/2) phosphorylate a
     variety of target proteins including, for example, several immediate-early
     gene products (e.g., Fos, Myc, and Jun family proteins). Certain
     phosphorylation reactions require binding of the MAP kinase to the DEF
     domain of the target protein. Inhibitors that block this interaction may
     be useful therapeutics for human disease, including as antineoplastic
     agents. This invention provides several advantages over known therapies
     that directly target the MAP kinase signaling cascade. Typically, most
     compds. that inhibit the MAP kinase pathway are non-specific and inhibit
     more than one enzyme, and the targeted inhibited kinases are not available
     to perform normal physiol. functions necessary for cell survival, whereas
     therapeutic methods of the present invention inhibit the activation of
     particular target proteins and leave the MAP kinases enzymically active
     and available to phosphorylate other non-DEF domain-containing proteins.
     Thus, DEF domains are identified in a large number of proteins, and the
     principles of the invention are exemplified using the immediate-early
     gene, c-Fos. Screening assays useful for identifying compds. that inhibit
     the MAP kinase-DEF domain interaction are also disclosed.
2005:71066   Document Number 142:170050  DEF domain-containing members of the MAP
     kinase pathway and their use in screening for drug inhibitors.  Blenis,
     John; Murphy, Leon O. (President and Fellows of Harvard College, USA).
     PCT Int. Appl. WO 2005007090 A2 20050127, 104 pp.  DESIGNATED STATES: W:
     AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO,
     CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR,
     HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,
     MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
     RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
     VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE,
     DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,
     TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2004-US21514
```

20040702. PRIORITY: US 2003-PV484761 20030703.

IT Proteins
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(BRC1 (breast **cancer** type 1), drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Addison's disease
Alzheimer's disease
Anaphylaxis
Anti-Alzheimer's agents
Anti-inflammatory agents
Anti-ischemic agents
Antiarthritics
Antiasthmatics
Anticonvulsants
Antidepressants
Antidiabetic agents
Antihypertensives
Antiobesity agents
Antiparkinsonian agents
Antipsychotics
Antirheumatic agents
Antitumor agents
Arthritis
Asthma
Atherosclerosis
Autoimmune disease
Carcinoma
Cardiovascular agents
Cardiovascular system, disease
Celiac disease
Cockayne's syndrome
Dermatitis
Dermatomyositis
Diabetes mellitus
Down's syndrome
Drug screening
Drug targets
Encephalitis
Epilepsy
Food allergy
Graves' disease
Hodgkin's disease
Human
Hypertension
Inflammation
Insomnia
Jaundice
Leukemia
Liver, disease
Lupus erythematosus
Mammary gland, **neoplasm**
Melanoma
Meningitis
Molecular association

Multiple sclerosis
Muscular dystrophy
Myasthenia gravis
**Neoplasm**
Nervous system agents
Neuroglia, **neoplasm**
Obesity
Ovary, **neoplasm**
Pancreas, **neoplasm**
Parkinson's disease
**Prostate** gland, **neoplasm**
Protein motifs
Rheumatic fever
Rheumatoid arthritis
Sarcoidosis
Schizophrenia
Signal transduction, biological
Sjogren's syndrome
Testis, **neoplasm**
Werner syndrome
(DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Proteins
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(DLC1 (deleted in liver **cancer** 1), drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT **Retinoic** acid receptors
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(RAR-α, drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT **Retinoic** acid receptors
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(RAR-γ, drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT **Retinoid** receptors
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(RORγ ( **retinoid** orphan receptor γ), drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Proteins
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(TEM8 (**tumor** endothelial marker 8), drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Kidney, **neoplasm**
(Wilms'; DEF domain-containing members of the MAP kinase pathway and their

use in screening for drug inhibitors)
IT Neuroglia, **neoplasm**
(astrocytoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Skin, **neoplasm**
(basal cell carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Biliary tract, **neoplasm**
(bile duct, carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT **Tumor** promoters
(bioassay comprising cells cultured with; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Animal cell line
(bioassay comprising cultured **tumor** cells; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Bladder, **neoplasm**
(carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Uterus, **neoplasm**
(cervix; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Intestine, **neoplasm**
(colon, carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Liver, **neoplasm**
(hepatoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Transformation, **neoplastic**
(immortalization, bioassay comprising cultured cells; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Proteins
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(large **tumor** suppressor 1, drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Adipose tissue, **neoplasm**
Sarcoma
(liposarcoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Brain, **neoplasm**
(medulloblastoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Nervous system, **neoplasm**
(meningioma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Astrocyte
(**neoplasm**, astrocytoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Meninges
(**neoplasm**, meningioma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)
IT Schwann cell

(**neoplasm**, schwannoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Nerve, **neoplasm**
(neuroblastoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Lung, **neoplasm**
(non-small-cell carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Bone, **neoplasm**
Sarcoma
(osteosarcoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Kidney, **neoplasm**
(renal cell carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Eye, **neoplasm**
(retinoblastoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Proteins
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**retinoic** acid-induced 1, drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Nervous system, **neoplasm**
(schwannoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Lung, **neoplasm**
(small-cell carcinoma; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT Antigens
RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**tumor**-associated, se2-1, drug target; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

IT 7722-84-1, Hydrogen peroxide, biological studies 9004-10-8, Insulin, biological studies **16561-29-8D**, Phorbol myristate acetate, derivs. 37353-31-4, Vanadate 61912-98-9, Insulin-like growth factor 62031-54-3, Fibroblast growth factor 62229-50-9, Epidermal growth factor 62683-29-8, Colony-stimulating factor 77238-39-2, Microcystin 78111-17-8, Okadaic acid 101932-71-2, Calyculin A 115926-52-8, PI3 kinase 117147-70-3, Amphiregulin 154531-34-7, Heparin-binding epidermal growth factor-like growth factor 196717-71-2, Epiregulin 301166-54-1, PTEN phosphatase
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(bioassay comprising cells cultured with; DEF domain-containing members of the MAP kinase pathway and their use in screening for drug inhibitors)

L4 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AB The present invention includes compns. and methods for treatment of **prostate cancer** which involve the use of 12-O-tetradecanoylphorbol-13-acetate combined with a **retinoid** such as all-**trans-retinoic** acid or **paclitaxel**

, wherein the drugs are administered together, and further wherein the combined use of these agents results in a synergistic effect on **prostate tumor** cell growth.

2004:220166 Document Number 140:247041 Compositions and methods for inhibiting proliferation in human **prostate cancer** cells. Conney, Allan H. (Rutgers, the State University, USA). PCT Int. Appl. WO 2004022001 A2 20040318, 25 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US28019 20030908. PRIORITY: US 2002-PV408568 20020906.

TI Compositions and methods for inhibiting proliferation in human **prostate cancer** cells

AB The present invention includes compns. and methods for treatment of **prostate cancer** which involve the use of 12-O-tetradecanoylphorbol-13-acetate combined with a **retinoid** such as all-**trans-retinoic** acid or **paclitaxel** , wherein the drugs are administered together, and further wherein the combined use of these agents results in a synergistic effect on **prostate tumor** cell growth.

ST **prostate cancer** inhibition tetradecanoylphorbol acetate **retinoid** combination; **paclitaxel** tetradecanoylphorbol acetate combination **prostate cancer** inhibition

IT Drug delivery systems
(carriers; compns. and methods for inhibiting proliferation in human **prostate cancer** cells using tetradecanoylphorbol-13-acetate in combination with **retinoid** or **paclitaxel**)

IT Antitumor agents
Human
**Prostate** gland, **neoplasm**
(compns. and methods for inhibiting proliferation in human **prostate cancer** cells using tetradecanoylphorbol-13-acetate in combination with **retinoid** or **paclitaxel**)

IT **Retinoids**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. and methods for inhibiting proliferation in human **prostate cancer** cells using tetradecanoylphorbol-13-acetate in combination with **retinoid** or **paclitaxel**)

IT Drug delivery systems
(diluents; compns. and methods for inhibiting proliferation in human **prostate cancer** cells using tetradecanoylphorbol-13-acetate in combination with **retinoid** or **paclitaxel**)

IT Drug interactions
(synergistic; compns. and methods for inhibiting proliferation in human **prostate cancer** cells using tetradecanoylphorbol-13-acetate in combination with **retinoid** or **paclitaxel**)

IT 302-79-4, all-**trans-Retinoic** acid **16561-29-8**
, 12-O-Tetradecanoylphorbol-13-acetate 33069-62-4, **Paclitaxel**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compns. and methods for inhibiting proliferation in human **prostate cancer** cells using tetradecanoylphorbol-13-acetate in combination with **retinoid** or **paclitaxel**)

L4 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 1

AB Clinically achievable concentrations of 12-O-tetradecanoylphorbol-13-acetate (TPA; 0.16-0.32 nM) and all-**trans-retinoic** acid (**ATRA**; 0.5-1 micro M) had a synergistic inhibitory effect on the growth of cultured LNCaP **prostate cancer** cells, and apoptosis was markedly stimulated. In additional studies, NCr immunodeficient mice received s.c. injection with LNCaP cells in Matrigel. After 4-6 weeks, mice with well-established **tumors** received i.p. injection with vehicle, TPA (0.16 nmol/g body weight), **ATRA** (0.5 nmol/g body weight), or TPA+**ATRA** in vehicle once a day for 46 days. **Tumor** growth occurred in all of the vehicle-treated control mice. The percentage of animals with some **tumor** regression after 21 days of treatment was 0% for the control group, 31% for the **ATRA** group, 62% for the TPA group, and 100% for the TPA+**ATRA** group (13 mice/group). Although treatment of the mice with TPA or TPA+**ATRA** continued to inhibit **tumor** growth for the duration of the 46-day study, treatment of the mice with **ATRA** alone did not inhibit **tumor** growth beyond 28 days of daily injections (6 mice/group). Mechanistic studies indicated that treatment of the mice with TPA or TPA+**ATRA** for 46 days increased apoptosis in the **tumors**, and treatment with TPA+**ATRA** also decreased the mitotic index. Because the dose of TPA used in this study was effective and resulted in clinically achievable blood levels, clinical trials with TPA alone or in combination with **ATRA** in patients with **prostate cancer** may be warranted.

2004105419. PubMed ID: 14996744. Inhibitory effect of 12-O-tetradecanoylphorbol-13-acetate alone or in combination with all-**trans-retinoic** acid on the growth of LNCaP **prostate tumors** in immunodeficient mice. Zheng Xi; Chang Richard L; Cui Xiao-Xing; Avila Gina E; Lee Sabrina; Lu Yao Ping; Lou You Rong; Shih Weichung Joe; Lin Yong; Reuhl Kenneth; Newmark Harold; Rabson Arnold; Conney Allan H. (Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, USA. ) Cancer research, (2004 Mar 1) 64 (5) 1811-20. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

TI Inhibitory effect of 12-O-tetradecanoylphorbol-13-acetate alone or in combination with all-**trans-retinoic** acid on the growth of LNCaP **prostate tumors** in immunodeficient mice.

AB Clinically achievable concentrations of 12-O-tetradecanoylphorbol-13-acetate (TPA; 0.16-0.32 nM) and all-**trans-retinoic** acid (**ATRA**; 0.5-1 micro M) had a synergistic inhibitory effect on the growth of cultured LNCaP **prostate cancer** cells, and apoptosis was markedly stimulated. In additional studies, NCr immunodeficient mice received s.c. injection with LNCaP cells in Matrigel. After 4-6 weeks, mice with well-established **tumors** received i.p. injection with vehicle, TPA (0.16 nmol/g body weight), **ATRA** (0.5 nmol/g body weight), or TPA+**ATRA** in vehicle once a day for 46 days. **Tumor** growth occurred in all of the vehicle-treated control mice. The percentage of animals with some **tumor** regression after 21 days of treatment was 0% for the control group, 31% for the **ATRA** group, 62% for the TPA group, and 100% for the TPA+**ATRA** group (13 mice/group). Although treatment of the mice with

TPA or TPA+**ATRA** continued to inhibit **tumor** growth for the duration of the 46-day study, treatment of the mice with **ATRA** alone did not inhibit **tumor** growth beyond 28 days of daily injections (6 mice/group). Mechanistic studies indicated that treatment of the mice with TPA or TPA+**ATRA** for 46 days increased apoptosis in the **tumors**, and treatment with TPA+**ATRA** also decreased the mitotic index. Because the dose of TPA used in this study was effective and resulted in clinically achievable blood levels, clinical trials with TPA alone or in combination with **ATRA** in patients with **prostate cancer** may be warranted.

CT Check Tags: Male
Animals
Apoptosis: DE, drug effects
Cell Division: DE, drug effects
**Cell Line, Tumor**
Drug Therapy, Combination
Mice
***Prostatic Neoplasms: DT, drug therapy**
**Prostatic Neoplasms: PA, pathology**
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Tetradecanoylphorbol Acetate: AD, administration & dosage
Tetradecanoylphorbol. . .

RN **16561-29-8 (Tetradecanoylphorbol Acetate)**; 302-79-4 (Tretinoin)

L4 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AB The invention provides compns. and methods for promoting apoptosis of **cancer** cells, and methods for treating **cancer**. The compns. comprise cyclin dependent kinase inhibitor and an agent that induces cellular differentiation. The methods of promoting apoptosis of **cancer** cells involve the co-administration to the **cancer** cells of a cyclin dependent kinase inhibitor and an agent that induces cell differentiation. The method for treating **cancer** involves the co-administration of a cyclin dependent kinase inhibitor and an agent that induces cellular differentiation to a patient. Examples of cellular differentiation agents include histone deacetylase inhibitors, protein kinase C activators, **retinoids**, and Vitamin D3.

2002:220378 Document Number 136:241653 Promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents. Grant, Steven; Dent, Paul; Rosato, Roberto; Cartee, Leanne (Virginia Commonwealth University, USA). PCT Int. Appl. WO 2002022133 A1 20020321, 62 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US28297 20010907. PRIORITY: US 2000-PV231885 20000912.

TI Promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents

AB The invention provides compns. and methods for promoting apoptosis of **cancer** cells, and methods for treating **cancer**. The compns. comprise cyclin dependent kinase inhibitor and an agent that induces cellular differentiation. The methods of promoting apoptosis of

**cancer** cells involve the co-administration to the **cancer** cells of a cyclin dependent kinase inhibitor and an agent that induces cell differentiation. The method for treating **cancer** involves the co-administration of a cyclin dependent kinase inhibitor and an agent that induces cellular differentiation to a patient. Examples of cellular differentiation agents include histone deacetylase inhibitors, protein kinase C activators, **retinoids**, and Vitamin D3.

ST promotion apoptosis **cancer** cell cyclin kinase inhibitor differentiation; **cancer** apoptosis cyclin dependent kinase inhibitor; cellular differentiation agent **cancer** apoptosis

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-2; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(D1; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E2F, interaction with Rb protein; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Mcl-1 (myeloid cell leukemia sequence-1); promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Rb; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(XIAP (X-linked inhibitor of apoptosis protein); promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Drug delivery systems
(carriers; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Histones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deacetylation of, inhibitors; promotion of apoptosis in **cancer**

cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(depsipeptides, histone deacetylation inhibitor; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Cell cycle
(disruption; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Cell differentiation
(inducers; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Mitochondria
(injury; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Antitumor agents
(leukemia; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Antitumor agents
(lymphoma; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Antitumor agents
(mammary gland; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Injury
(mitochondrial; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Antitumor agents
(myeloma; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Mammary gland
**Prostate** gland
(**neoplasm**, inhibitors; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Deacetylation
(of histone, inhibitors; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Cyclin dependent kinase inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p21CIP1; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Cyclin dependent kinase inhibitors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p27KIP1; promotion of apoptosis in **cancer** cells by

co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Antitumor agents
Apoptosis
Drug interactions
Human
(promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT **Retinoids**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT Antitumor agents
(**prostate** gland; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 137632-07-6, ERK1 kinase 137632-08-7, ERK2 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activation; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 141436-78-4, Protein kinase C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(activators; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 96-48-0, Butyrolactone 101622-51-9, Olomoucine 112953-11-4, UCN-01 146426-40-6, Flavopiridol 186692-46-6, Roscovitine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclin dependent kinase inhibitor; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 156-54-7, Sodium butyrate 4346-18-3, Phenylbutyrate 58880-19-6, Trichostatin A 112522-64-2, CI-994 149647-78-9 209783-80-2, MS 275
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(histone deacetylase inhibitor; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 9076-57-7, Histone deacetylase 150428-23-2, Cyclin dependent kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 9007-43-6, Cytochrome C, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(mitochondrial release; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT 201556-11-8, Procaspase 3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation

agents)

IT 67-97-0, Vitamin D3 302-79-4, all-**trans**-**Retinoic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

IT **16561-29-8**, PMA 100629-51-4, Bryostatin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein kinase C activator; promotion of apoptosis in **cancer** cells by co-administration of cyclin dependent kinase inhibitors and cellular differentiation agents)

L4 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AB Drug discovery strategies are needed that can rapidly exploit multiple therapeutic targets associated with the complex gene expression changes that characterize a polygenic disease such as **cancer**. We report a new cell-based high-throughput technol. for screening chemical libraries against several potential **cancer** target genes in parallel. Multiplex gene expression (MGE) anal. provides direct and quant. measurement of multiple endogenous mRNAs using a multiplexed detection system coupled to reverse transcription-PCR. A multiplex assay for six genes over-expressed in **cancer** cells was used to screen 9000 chems. and known drugs in the human **prostate cancer** cell line PC-3. Active compds. that modulated gene expression levels were identified, and IC50 values were determined for compds. that bind DNA, cell surface receptors, and components of intracellular signaling pathways. A class of steroids related to the cardiac glycosides was identified that potently inhibited the plasma membrane Na+K+-ATPase resulting in the inhibition of four of the **prostate** target genes including transcription factors Hoxb-13, hPSE/PDEF, hepatocyte nuclear factor-3α, and the inhibitor of apoptosis, survivin. Representative compds. selectively induced apoptosis in PC-3 cells compared with the non-metastatic cell line BPH-1. The multiplex assay distinguished potencies among structural variants, enabling structure-activity anal. suitable for chemical optimization studies. A second multiplex assay for five toxicol. markers, Hsp70, Gadd153, Gadd45, O6-methylguanine-DNA methyltransferase, and cyclophilin, detected compds. that caused DNA damage and cellular stress and was a more sensitive and specific indicator of potential toxicity than measurement of cell viability. MGE anal. facilitates rapid drug screening and compound optimization, the simultaneous measurement of toxicol. end points, and gene function anal.

2003:61264 Document Number 139:143215 Multiplex gene expression analysis for high-throughput drug discovery: screening and analysis of compounds affecting genes over-expressed in **cancer** cells. Johnson, Paul H.; Walker, Roger P.; Jones, Steven W.; Stephens, Kathy; Meurer, Janet; Zajchowski, Deborah A.; Luke, May M.; Eeckman, Frank; Tan, Yuping; Wong, Linda; Parry, Gordon; Morgan, Thomas K., Jr.; McCarrick, Meg A.; Monforte, Joseph (Department of Cancer Research, Berlex Biosciences, Richmond, CA, 94804-0099, USA). Molecular Cancer Therapeutics, 1(14), 1293-1304 (English) 2002. CODEN: MCTOCF. ISSN: 1535-7163. Publisher: American Association for Cancer Research.

TI Multiplex gene expression analysis for high-throughput drug discovery: screening and analysis of compounds affecting genes over-expressed in **cancer** cells

AB . . . can rapidly exploit multiple therapeutic targets associated with the complex gene expression changes that characterize a polygenic disease such as **cancer**. We report a new cell-based high-throughput technol. for screening chemical libraries against several potential **cancer** target genes in parallel. Multiplex gene expression (MGE) anal. provides direct and quant. measurement of multiple endogenous mRNAs using a multiplexed detection system coupled to reverse transcription-PCR. A multiplex assay for six genes over-expressed in **cancer** cells was used to screen 9000 chems. and known drugs in the human **prostate cancer** cell line PC-3. Active compds. that modulated gene expression levels were identified, and IC50 values were determined for compds. that. . . the cardiac glycosides was identified that potently inhibited the plasma membrane Na+K+-ATPase resulting in the inhibition of four of the **prostate** target genes including transcription factors Hoxb-13, hPSE/PDEF, hepatocyte nuclear factor-3α, and the inhibitor of apoptosis, survivin. Representative compds. selectively induced. . .

ST multiplex gene expression high throughput screening antitumor **prostate**

IT Human
**Prostate** gland, **neoplasm**
Signal transduction, biological
(multiplex gene expression anal. for high-throughput drug discovery)

IT 50-07-7, Mitomycin C 50-23-7, Hydrocortisone 50-28-2, β-Estradiol; biological studies 50-76-0, Dactinomycin 53-79-2, Puromycin 54-62-6, Aminopterin 57-62-5 64-86-8, Colchicine 66-81-9, Cycloheximide 71-63-6, Digitoxin 83-79-4, Rotenone 83-89-6, Quinacrine 107-92-6, Butyric acid, biological studies 143-67-9, Vinblastine sulfate 302-79-4, **Retinoic** acid 472-26-4 483-18-1, Emetine 508-52-1 518-28-5, Podophyllotoxin 630-60-4, Ouabain 639-13-4 1178-61-6 1397-94-0, Antimycin A 1405-97-6, Gramicidin **16561-29-8**, Phorbol 12-myristate 13-acetate 22144-77-0, Cytochalasin D 53123-88-9, Rapamycin 58880-19-6, Trichostatin A 66575-29-9, Forskolin 154447-36-6, LY294002 569682-35-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multiplex gene expression anal. for high-throughput drug discovery)

L4 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 2

AB The active form of vitamin D(3), 1,25(OH)(2)D(3), inhibits proliferation and induces differentiation of a variety of malignant cells. A new class of vitamin D(3) analogs, having 2 identical side chains attached to carbon-20, was synthesized and the anticancer effects evaluated. Four analogs were evaluated for their ability to inhibit growth of myeloid leukemia (NB4, HL-60), breast (MCF-7), and **prostate** (LNCaP) **cancer** cells. All 4 analogs inhibited growth in a dose-dependent manner. Most effective was 21-(3-methyl-3-hydroxy-butyl)-19-nor D(3) (Gemini-19-nor), which has 2 side chains and removal of the C-19. Gemini-19-nor was approximately 40 625-, 70-, 23-, and 380-fold more potent than 1,25(OH)(2)D(3) in inhibiting 50% clonal growth (ED(50)) of NB4, HL-60, MCF-7, and LNCaP cells, respectively. Gemini-19-nor (10(-8) M) strongly induced expression of CD11b and CD14 on HL-60 cells (90%); in contrast, 1,25(OH)(2)D(3) (10(-8) M) stimulated only 50% expression. Annexin V assay showed that Gemini-19-nor and 1,25(OH)(2)D(3) induced apoptosis in a dose-dependent fashion. Gemini-19-nor (10(-8) M, 4 days) caused apoptosis in approximately 20% of cells, whereas 1,25(OH)(2)D(3) at the same concentration did not induce apoptosis. Gemini-19-nor increased

in HL-60 both the proportion of cells in the G(1)/G(0) phase and expression level of p27(kip1). Moreover, Gemini-19-nor stimulated expression of the potential **tumor** suppressor, PTEN. Furthermore, other inducers of differentiation, all-**trans-retinoic** acid and 12-O-tetradecanoylphorbol 13-acetate, increased PTEN expression in HL-60. In summary, Gemini-19-nor strongly inhibited clonal proliferation in various types of **cancer** cells, especially NB4 cells, suggesting that further studies to explore its anticancer potential are warranted. In addition, PTEN expression appears to parallel terminal differentiation of myeloid cells.

2001287310. PubMed ID: 11290607. Novel vitamin D(3) analog, 21-(3-methyl-3-hydroxy-butyl)-19-nor D(3), that modulates cell growth, differentiation, apoptosis, cell cycle, and induction of PTEN in leukemic cells. Hisatake J; O'Kelly J; Uskokovic M R; Tomoyasu S; Koeffler H P. (Division of Hematology/Oncology, Cedars-Sinai Medical Center, UCLA School of Medicine, Los Angeles, CA 90048, USA. ) Blood, (2001 Apr 15) 97 (8) 2427-33. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB . . . effects evaluated. Four analogs were evaluated for their ability to inhibit growth of myeloid leukemia (NB4, HL-60), breast (MCF-7), and **prostate** (LNCaP) **cancer** cells. All 4 analogs inhibited growth in a dose-dependent manner. Most effective was 21-(3-methyl-3-hydroxy-butyl)-19-nor D(3) (Gemini-19-nor), which has 2 side. . . the proportion of cells in the G(1)/G(0) phase and expression level of p27(kip1). Moreover, Gemini-19-nor stimulated expression of the potential **tumor** suppressor, PTEN. Furthermore, other inducers of differentiation, all-**trans-retinoic** acid and 12-O-tetradecanoylphorbol 13-acetate, increased PTEN expression in HL-60. In summary, Gemini-19-nor strongly inhibited clonal proliferation in various types of **cancer** cells, especially NB4 cells, suggesting that further studies to explore its anticancer potential are warranted. In addition, PTEN expression appears. . .

CT Check Tags: Comparative Study; Female; Male
Antineoplastic Agents: CH, chemistry
Antineoplastic Agents: PD, pharmacology
Apoptosis: DE, drug effects
**Breast Neoplasms: PA, pathology**
Calcitriol: AA, analogs & derivatives
Calcitriol: CH, chemistry
*Calcitriol: PD, pharmacology
Carcinoma: PA, pathology
Cell Cycle:. . . Cell Differentiation: DE, drug effects
Cell Division: DE, drug effects
Dose-Response Relationship, Drug
*Gene Expression Regulation, Leukemic: DE, drug effects
**Gene Expression Regulation, Neoplastic: DE, drug effects**
HL-60 Cells: DE, drug effects
HL-60 Cells: ME, metabolism
Humans
Leukemia, Myeloid: PA, pathology
Microtubule-Associated Proteins: BI, biosynthesis
Microtubule-Associated Proteins: GE, genetics
***Neoplasm Proteins: BI, biosynthesis**
**Neoplasm Proteins: GE, genetics**
*Phosphoric Monoester Hydrolases: BI, biosynthesis
Phosphoric Monoester Hydrolases: GE, genetics
**Prostatic Neoplasms: PA, pathology**

Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
Structure-Activity Relationship
Tetradecanoylphorbol Acetate: PD, pharmacology
Tretinoin: PD, pharmacology
**Tumor Cells, Cultured: DE, drug effects**
***Tumor Suppressor Proteins**

RN 147604-94-2 (cyclin-dependent kinase inhibitor p27); **16561-29-8 (Tetradecanoylphorbol Acetate)**; 302-79-4 (Tretinoin); 32222-06-3 (Calcitriol)

CN 0 (21-(3-methyl-3-hydroxybutyl)-19-norvitamin D3); 0 (Antineoplastic Agents); 0 (Cell Cycle Proteins); 0 (Microtubule-Associated Proteins); 0 (**Neoplasm** Proteins); 0 (**Tumor** Suppressor Proteins); EC 3.1.3 (Phosphoric Monoester Hydrolases); EC 3.1.3.48 (PTEN protein)

L4 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 3

AB c-Raf-1 (Raf-1) is a central component of signal transduction pathways stimulated by various growth factors, protein kinase C, and other protein kinases. Raf-1 activation is thought to be initiated at the plasma membrane after its recruitment by Ras. Raf-1 activation is associated primarily with proliferation and cell survival, but it has also been implicated in apoptosis. Raf-1 has also been shown to form complexes with both R-Ras and Bcl-2, raising the possibility that this component of cellular Raf-1 plays a role in apoptosis. Recently, taxol was reported to induce Bcl-2 phosphorylation and inactivation. We have previously demonstrated Raf-1 activation following taxol in MCF7 cells. We now present evidence that taxol fails to stimulate either apoptosis or phosphorylation of Bel-2 in the absence of Raf-1. Moreover, Raf-1 activation by taxol coincided with Bel-2 phosphorylation, showing similar dose and time dependence. Thus, our data support a role for a distinct subcellular component of Raf-1, which is taxol but not phorbol myristate acetate sensitive, in mediating an apoptotic pathway involving Bcl-2.

96184978. PubMed ID: 8620503. Taxol-induced apoptosis and phosphorylation of Bcl-2 protein involves c-Raf-1 and represents a novel c-Raf-1 signal transduction pathway. Blagosklonny M V; Schulte T; Nguyen P; Trepel J; Neckers L M. (Clinical Pharmacology Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892, USA. ) Cancer research, (1996 Apr 15) 56 (8) 1851-4. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

CT Check Tags: Female; Male
*Antineoplastic Agents, Phytogenic: TO, toxicity
*Apoptosis: DE, drug effects
Apoptosis: PH, physiology
**Breast Neoplasms**
Cell Line
Enzyme Activation
HL-60 Cells
Humans
***Paclitaxel: TO, toxicity**
Phosphorylation
**Prostatic Neoplasms**
Protein-Serine-Threonine Kinases: IP, isolation & purification
*Protein-Serine-Threonine Kinases: ME, metabolism
Proto-Oncogene Proteins: IP, isolation & purification
*Proto-Oncogene Proteins: ME, metabolism
Proto-Oncogene Proteins c-bcl-2

Proto-Oncogene Proteins c-raf
*Signal Transduction
Tetradecanoylphorbol Acetate: PD, pharmacology
**Tumor Cells, Cultured**
RN **16561-29-8 (Tetradecanoylphorbol Acetate); 33069-62-4 (Paclitaxel)**

L4 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 4
AB Liarozole reduced **tumor** growth in the androgen-dependent Dunning-G and the androgen-independent Dunning MatLu rat **prostate** carcinoma models as well as in patients with metastatic **prostate cancer** who had relapsed after orchiectomy. In vitro, liarozole did not have cytostatic properties, as measured by cell proliferation in breast MCF-7 and **prostate** DU145 and LNCaP carcinoma cell lines. It did not alter the metabolism of labeled testosterone i.e. the 5 alpha-reductase in cultured rat **prostatic** cells. In mouse F9 teratocarcinoma cells liarozole did not show any **retinoid**-like properties but enhanced the plasminogen activator production induced by **retinoic** acid. Furthermore, liarozole and **retinoic** acid similarly reduced the growth of the androgen-dependent Dunning-G **tumor** in nude mice and inhibited **tumor** promotion elicited by phorbol ester in mouse skin. These data have raised the hypothesis that the antitumoral properties of liarozole may be related to inhibition of **retinoic** acid degradation, catalyzed by a P-450-dependent enzyme that is blocked by the drug.
92399299. PubMed ID: 1525060. Experimental studies with liarozole (R 75,251): an antitumoral agent which inhibits **retinoic** acid breakdown. De Coster R; Wouters W; Van Ginckel R; End D; Krekels M; Coene M C; Bowden C. (Janssen Research Foundation, Beerse, Belgium. ) Journal of steroid biochemistry and molecular biology, (1992 Sep) 43 (1-3) 197-201. Ref: 13. Journal code: 9015483. ISSN: 0960-0760. Pub. country: ENGLAND: United Kingdom. Language: English.
TI Experimental studies with liarozole (R 75,251): an antitumoral agent which inhibits **retinoic** acid breakdown.
AB Liarozole reduced **tumor** growth in the androgen-dependent Dunning-G and the androgen-independent Dunning MatLu rat **prostate** carcinoma models as well as in patients with metastatic **prostate cancer** who had relapsed after orchiectomy. In vitro, liarozole did not have cytostatic properties, as measured by cell proliferation in breast MCF-7 and **prostate** DU145 and LNCaP carcinoma cell lines. It did not alter the metabolism of labeled testosterone i.e. the 5 alpha-reductase in cultured rat **prostatic** cells. In mouse F9 teratocarcinoma cells liarozole did not show any **retinoid**-like properties but enhanced the plasminogen activator production induced by **retinoic** acid. Furthermore, liarozole and **retinoic** acid similarly reduced the growth of the androgen-dependent Dunning-G **tumor** in nude mice and inhibited **tumor** promotion elicited by phorbol ester in mouse skin. These data have raised the hypothesis that the antitumoral properties of liarozole may be related to inhibition of **retinoic** acid degradation, catalyzed by a P-450-dependent enzyme that is blocked by the drug.
CT Animals
*Antineoplastic Agents: PD, pharmacology
Cell Division: DE, drug effects
Humans
*Imidazoles: PD, pharmacology
**Neoplasms, Experimental: DT, drug therapy**

**Neoplasms, Experimental: ME, metabolism**
Plasminogen Activators: ME, metabolism
Testosterone: ME, metabolism
Tetradecanoylphorbol Acetate: PD, pharmacology
*Tretinoin: ME, metabolism
RN 115575-11-6 (liarozole); **16561-29-8 (Tetradecanoylphorbol Acetate)** ; 302-79-4 (Tretinoin); 58-22-0 (Testosterone)

L4 ANSWER 9 OF 9 CANCERLIT on STN
AB The specific role of the cell membrane in mediating the activity of lipophilic differentiation effectors is relatively unclear. It is possible to modulate **tumor** promoter (eg, 12-O-tetradecanoylphorbol 13-acetate [TPA]-activated protein kinase C [PKC]) activity in many different ways. This activity has been related to changes in **tumor** cell growth and differentiation in many tissue culture systems. Vitamin D3, like phorbol ester **tumor** promoters, can induce terminal monocyte/macrophage differentiation of HL-60 cells and can upregulate phorbol ester receptors/PKC in HL-60 cells. However, in the HL-60 cell culture system, both the kinetics of the differentiation response and the markers for the final differentiated phenotype are notably different for vitamin D3 and phorbol esters. At physiologic concentrations **retinoids** alter cell surface characteristics through cell surface effects on differentiation. **Retinoids** can inhibit the development of epithelial **tumorigenesis** in different tissues including the lung, bladder, **prostate**, mammary epithelia, and epidermis. **Retinoic** acid (RA) may control differentiation through its effects on the expression of genes coding for proteins of the extracellular matrix and/or their cell surface receptors. The discovery of nuclear receptors for RA as transcriptional activations has opened new avenues in **retinoid** research. Short-chain fatty acids (FAs), most notably butyrate, are well-known differentiation effectors in various cell culture systems. Longer-chain fatty acids as single agents have been reported not to produce direct effects on leukemic cell differentiation and thus cannot be considered differentiation inducers per se, although membrane-associated long-chain FAs most likely play an important role in differentiation processes. Vitamin D3 has been reported to induce sphingomyelinase activity in HL-60 cells; the endogenous products of this enzyme can synergize with the subinducing concentrations of vitamin D3 to effect monocytic differentiation. In another study, exogenous sphingomyelinase activity augmented the level of sphingoid bases in HL-60 cells, leading to inhibition of PKC activity and inhibition of TPA-induced, but not vitamin D3-induced, monocytic differentiation of HL-60 cells. Taken together, these data underscore the differences in differentiation-inducing pathways of phorbol esters and vitamin D3. (102 Refs)
92680100 Document Number: 92680100. MEMBRANE EVENTS REGULATING DIFFERENTIATION IN RESPONSE TO LIPOPHILIC INDUCING AGENTS: THERAPEUTIC IMPLICATIONS. Gallagher R E; De Luca L M. (Div. of Oncology, Montefiore Hosp., Bronx, NY 10467. ) Serono Symp Publ Raven Press, (1991) 82 143-57. Language: English.
AB . . . of the cell membrane in mediating the activity of lipophilic differentiation effectors is relatively unclear. It is possible to modulate **tumor** promoter (eg, 12-O-tetradecanoylphorbol 13-acetate [TPA]-activated protein kinase C [PKC]) activity in many different ways. This activity has been related to changes in **tumor** cell growth and differentiation in many tissue culture systems. Vitamin D3, like phorbol ester **tumor** promoters, can induce terminal

monocyte/macrophage differentiation of HL-60 cells and can upregulate phorbol ester receptors/PKC in HL-60 cells. However, in. . . and the markers for the final differentiated phenotype are notably different for vitamin D3 and phorbol esters. At physiologic concentrations **retinoids** alter cell surface characteristics through cell surface effects on differentiation. **Retinoids** can inhibit the development of epithelial **tumorigenesis** in different tissues including the lung, bladder, **prostate**, mammary epithelia, and epidermis. **Retinoic** acid (RA) may control differentiation through its effects on the expression of genes coding for proteins of the extracellular matrix. . . and/or their cell surface receptors. The discovery of nuclear receptors for RA as transcriptional activations has opened new avenues in **retinoid** research. Short-chain fatty acids (FAs), most notably butyrate, are well-known differentiation effectors in various cell culture systems. Longer-chain fatty acids. . .

RN **16561-29-8 (Tetradecanoylphorbol Acetate)**; 32222-06-3 (Calcitriol); 9007-34-5 (Collagen)

CN EC 2.7.1.- (Protein Kinase C); 0 (Fatty Acids); 0 (Glycosphingolipids); 0 (Laminin); 0 (Membrane Lipids); 0 (Phorbol Esters); 0 (**Retinoids**)

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| L1 | 13490 | tpa | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:26 |
| L2 | 0 | 1 and all same tran$2 same retinoic same acid | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:27 |
| L3 | 1673 | 1 and prostate same (cancer$ or tumor$ or tumour$ or neoplas$) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:37 |
| L4 | 729 | 3 and (retinoid or retinoic or atra) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:37 |
| L5 | 496 | 12-o-tetradecanoylphorbol-13-acetat$ 2 | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:37 |
| L6 | 142 | 5 and prostate same (cancer$ or tumor$ or tumour$ or neoplas$) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:37 |
| L7 | 83 | 6 and (retinoid or retinoic or atra) | US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT | OR | ON | 2005/03/03 21:37 |